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ORIGINAL ARTICLE

Correlations in post-mortem imaging-histopathology studies of sporadic human cerebral small vessel disease: A systematic review

Catherine A. Humphreys[1] | Colin Smith[1] | Joanna M. Wardlaw[1,2,3]

[1]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

[2]UK Dementia Research Institute at The University of Edinburgh, Edinburgh, UK

[3]Row Fogo Centre for Research into Ageing and the Brain, Edinburgh, UK

Correspondence
Catherine A. Humphreys, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.
Email: catherine.humphreys@nhslothian.scot.nhs.uk

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Abstract

Aims: Sporadic human cerebral small vessel disease (SVD) commonly causes stroke and dementia but its pathogenesis is poorly understood. There are recognised neuroimaging and histopathological features. However, relatively few studies have examined the relationship between the radiological and pathological correlates of SVD; better correlation would promote greater insight into the underlying biological changes.

Methods: We performed a systematic review to collate and appraise the information derived from studies that correlated histological with neuroimaging-defined SVD lesions. We searched for studies describing post-mortem imaging and histological tissue examination in adults, extracted data from published studies, categorised the information and compiled this narrative.

Results: We identified 38 relevant studies, including at least 1146 subjects, 342 of these with SVD: 29 studies focussed on neuroradiological white matter lesions (WML), six on microinfarcts and three on dilated perivascular spaces (PVS) and lacunes. The histopathology terminology was diverse with few robust definitions. Reporting and methodology varied widely between studies, precluding formal meta-analysis. PVS and 'oedema' were frequent findings in WML, being described in at least 94 and 18 radiological WML, respectively, in addition to myelin pallor. Histopathological changes extended beyond the radiological lesion margins in at least 33 radiological WML. At least 43 radiological lesions not seen pathologically and at least 178 histological lesions were not identified on imaging.

Conclusions: Histopathological assessment of human SVD is hindered by inconsistent methodological approaches and unstandardised definitions. The data from this systematic review will help to develop standardised definitions to promote consistency in human SVD research.

KEYWORDS
cerebral small vessel disease, neuroimaging, neuropathology, radiology, systematic review, vascular dementia

INTRODUCTION

Sporadic cerebral small vessel disease (SVD) is a common finding in the ageing brain, defined by neuroimaging features [1] and a range of histological lesions [2,3]. While critical to providing a uniform structure to future research, where histopathological definitions are defined, particularly Skrobot et al. [2], there is no attempt at gradation, and they are defined in the context of a single clinical outcome, cognitive decline. Clinically significant, SVD causes 25% of ischaemic strokes [3] and 85% of intracerebral haemorrhage [4]. It is the major cause of vascular dementia (VaD) [5] and is associated with a range of other cognitive [6,7] and physical problems [8,9].

Small vessel disease is best visualised in vivo using magnetic resonance imaging (MRI). An international working group from the Centres of Excellence in Neurodegeneration developed definitions and imaging standards for markers and consequences of SVD identifying white matter hyperintensities (WMH), lacunes, enlarged perivascular spaces (PVS), microbleeds and at high field, microinfarcts [1,10].

Currently, there is no comparable consensus document regarding histological SVD lesions [11]. Variation between MRI appearances and histopathology may reflect this lack of consistency in definitions or may be a consequence of the scarcity of studies detailing the pathology of imaging-detected lesions [12]. Additionally, early stage disease may be under-reported and most autopsy-identified lesions may be end-stage 'scars' [13]. Genetic abnormalities and molecular pathways [14,15] have been identified, reflecting the heterogeneous underlying pathophysiology [16]. Potential mechanisms for vascular and tissue damage include blood–brain barrier (BBB) dysfunction [17,18], para- and peri-vascular space abnormalities [19,20] and abnormal perfusion [21,22]. However, precise mechanisms at different stages and in different lesions remain unclear.

Some lesions are clearly identified by both MRI and histology, such as lacunes [2], PVS [23] and small infarcts [24]. Others, like early stage WMH, are easily observed on MRI but difficult to detect histologically, contributing to apparent discrepancies about lesion composition, notably water content and axon degeneration when assessed by histology and MRI respectively. Damaged micro-vessels (i.e. arteriolosclerosis, lipohyalinosis, fibrinoid necrosis and cerebral amyloid angiopathy [CAA]) are below current imaging resolution thresholds [2,25,26], but are key descriptors in histological assessment.

Detailed imaging-histological correlations, particularly of individual lesions and subtypes, are required. We aimed to summarise current knowledge of precise MRI-histological correlations in common SVD lesions, to assess their reliability and generalisability and identify where greater consistency in methodology and definition is needed.

METHODS

In this systematic review, we identified all studies correlating ex vivo medical imaging with histopathology of SVD lesions. Given the dynamic nature of SVD during life, we focused on studies that used ex vivo imaging to avoid extended timelines between imaging and histology.

Search terms

We searched for the terms 'small vessel disease', 'SVD' and all relevant commonly used neuroradiological [1] and histopathological terms (Table 1), in the Medline online database from its inception in 1966 to the 9 September 2020. The search terms were refined through several iterations to ensure all relevant SVD lesions on imaging and histology were included, and that all potential lesion types were included (Table 1). We hand-searched reference lists in textbooks, review papers and two relevant journals (*Stroke* and *Neuropathology and Applied Neurobiology*) and for relevant primary publications.

Inclusion/exclusion criteria

We included all studies published in full which carried out post-mortem computerised tomography (CT) or MR imaging and histological examination of adult human brain tissue to study sporadic SVD (Figure 1). We excluded: studies reporting only biopsy material; studies performing post-mortem imaging but no histopathology or vice versa; studies not reporting on human sporadic SVD; non-English publications; and studies of haemorrhagic SVD lesions only as these were reviewed recently [27,28]. We excluded all duplicate publications, editorials and conference abstracts. Where studies came from the same groups and it was not clear which, if any, cases were included more than once, we included only the largest study for subject characteristics and results, and only distinct individual findings from the other papers.

Quality of reporting

To assess methodology quality, we adapted the Standards for the Reporting of Diagnostic Accuracy studies (STARD) criteria [29] for observational studies to give a score out of 25. Information was extracted regarding the authors expertise, aims, the study population, study dates, data collection, participant recruitment, pathological and radiological methods, blinding, analysis, results reporting and discussion of findings (Table 2). Each individual feature could gain one point, or part thereof if only part of the criteria was met. The authors discussed and resolved uncertainties regarding inclusion, exclusion and scoring when required.

Data extraction

Data were extracted from study characteristics including study design and dates, prospective or retrospective recruitment, data

TABLE 1 Final search strategy

Results	Search
1	exp Brain/pa, pp [Pathology, Physiopathology]
2	*Cerebrovascular Disorders/pa [Pathology]
3	*Stroke, Lacunar/et, pa, pp [Etiology, Pathology, Physiopathology]
4	(cerebrovascular disease or cerebrovascular lesions or cerebrovascular pathology).ti,ab.
5	SVD.ti,ab.
6	small vessel disease.ti,ab.
7	lipohyalinosis.ti,ab.
8	arteriolosclerosis.ti,ab.
9	(atherosclerosis adj3 small*).ti,ab.
10	CAA.ti,ab.
11	cerebral amyloid angiopathy.ti,ab.
12	(WMH or white matter hyperintensit$).ti,ab.
13	(WML or white matter lesion$).ti,ab.
14	((lacune or lacunar) adj2 (stroke or infarct$)).ti,ab.
15	microbleed.ti,ab.
16	perivascular space.ti,ab.
17	leukoaraiosis.ti,ab.
18	small deep infarct.ti,ab.
19	fibrinoid necrosis.ti,ab.
20	(histopatholog$ or histolog$ or patholog$).ti,ab.
21	(IHC or immunohistochemi$).ti,ab.
22	(ICC or immunocytochemi$).ti,ab.
23	1 or 2 or 3
24	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
25	20 or 21 or 22
26	23 and 24 and 25
27	limit 26 to humans

collected, sample size, blinding and analysis methods. Subject data included demographic and clinical data including cognitive status, in vivo investigations, age, gender and ethnicity. Radiological specifics included scanner field strength, sequence resolution, tissue scanned, measures to avoid artefact and involvement of neuroradiologists. We collected details of pathological processing, assessment of tissue quality, macroscopic examination, staining, grading systems used, terminology and definitions and involvement of neuropathologists. All three authors read the papers and had regular meetings to agree a consistent approach and achieved consensus through discussion.

Various pathological terminologies were used in the papers, not always consistently, hence we condensed the information into manageable categories based on the terminologies in each paper. For reference, we provide a full list of the terms encountered and similar expressions in Table S1. We recorded the method used to relate tissue locations on MRI/CT to that on histology, the analyses used and the neuroradiological–neuropathological findings.

RESULTS

The initial search yielded 1627 articles: 16 duplicates were removed, and we excluded 1403 papers including 37 studying monogenic SVD (reasons detailed in Figure 1). For interest, the excluded papers that studied monogenic SVD are listed in the supplement, two of which compared lesion appearances on post-mortem imaging and histology [30,31]. Searching reference lists of 183 review papers provided nine additional relevant papers, and two further papers were identified from hand-searching journals. This resulted in 38 relevant papers, that reported imaging of at least 1146 individual patients in total, 342 of whom had SVD lesions on imaging. Studies were published between 1986 and September 2020, all using ex vivo MRI (Table 3). Of these we created three groups; 29 primarily focused on imaging-identified white matter lesions (WML), six studying microinfarcts and three on PVS and lacunes.

The information provided varied between studies. There were insufficient numerical data to perform a meta-analysis. Only one group clarified subject duplication between papers [32,33]. We

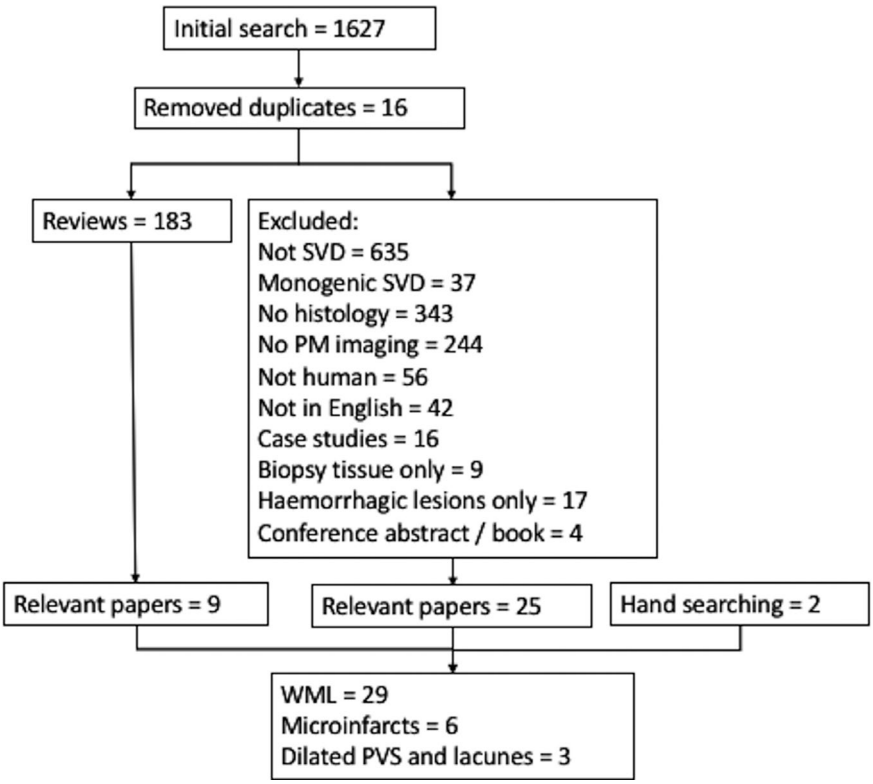

FIGURE 1 Summary of a literature evaluation. PVS perivascular spaces; SVD, small vessel disease

included only the largest study when there was possible duplication and it was not possible to extract precise subject data.

Study quality

The mean quality score was 14/25 (range 6–19) (Table 3; Figure 2). Study aims, radiological definitions, statistical analysis, distribution of severity and discussing the scientific importance were well reported, and all papers described some degree of radiological methodology. Study dates, participant recruitment methods, tissue quality assessment, blinding of radiological assessment and addressing radiological artefact were not consistently reported. One study reported participants' race (all female Caucasians) [34]. None reported tissue quality assessment beyond recording post-mortem interval (PMI) to autopsy.

Study characteristics

Subjects and SVD lesions

Of the 38 papers identified, 28 studied WML based on the MRI-identified WMHs, one additional study compared white matter MRI diffusion tensor imaging (DTI) changes with histological measures and was included here. Six studied microinfarcts, and three studied PVS and lacunes.

The WMH/WML studies were from 21 groups in 11 countries (Table 3). They included at least 895 subjects, (at least 277 of whom were female) aged 45–101, at least 313 of these had SVD on imaging.

The microinfarct studies were from four groups in different countries, including at least 202 subjects [35–40]. Four papers directly compared lesions identified on MRI with histology [37–40]. At least 19/202 subjects had microinfarcts although it was not possible to determine how many had lesions in two papers [35,36]. The age range was 62–98 years in the three papers where age could be calculated or was given [37,39,40].

The studies reporting on PVS and lacunes were from different groups [33,41,42] and included 53 subjects in total, although four subjects [42] also appear to have been reported in a paper studying microinfarcts [39]. Ten subjects had PVS and/or lacunes, six of these were female. Ages ranged from 37 to 90 years.

Haemorrhagic pathology identified within the studies included is not reported here because it was not consistently reported, particularly where it was not the focus of a paper. Recent detailed reviews of haemorrhagic SVD pathology have been published and better serve to describe the relevant lesions [27,28].

Data collection

Twelve studies collected subjects' data retrospectively (Table 3; Figure 2) from different, often multiple, sources including medical notes [37–39,41–49], cause of death (not specifically stated where these data were obtained) [37,44,48–50], autopsy reports [38,39,44,45] and interviewing relatives [46]. Many did not report how or when subject data were collected [32,33,35,36,40,51–58]. Ten studies collected clinical information prospectively [34,59–67], and one provided no subject information [68].

TABLE 2 Quality assessment

Title	Neuropathologist and neuroradiologist in the authors
Introduction	State the research questions or study aims
Methods	
Participants	Describe the study population: inclusion and exclusion criteria, setting and locations where the data were collected Report when the study was done, including beginning and ending dates of recruitment Describe participant recruitment Describe data collection: prospective or retrospective
Pathology	Describe the pathological methods: rationale, technical specifications (and/or cite references) Define pathological lesions and criteria used for assessments Describe the number and expertise of the persons executing the macroscopic and microscopic neuropathological assessment Were the individuals carrying out the macroscopic and microscopic assessment blinded to the results of other assessments and any other available information? Assess PM tissue quality and/or report post-mortem interval
Imaging	Describe the radiological methods: rationale, technical specifications (and/or cite references) Define radiological lesions and criteria used for assessments Describe the number and expertise of the persons executing the radiological assessment Were the assessors blinded to the results of other assessments and any other available information? Describe measures taken to minimise artefact on MRI
Statistics	Describe statistical methods for calculating or comparing measures of diagnostic accuracy, adjusting for variables, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals)
Results	
Participants	Report clinical and demographic characteristics of the study population (e.g. age, sex, race, clinical info etc.) Report characteristics for individual subjects Report clinical features associated with SVD
Results	Report the distribution of disease severity Report a cross-tabulation (including indeterminate and missing results)
Discussion	Discuss the clinical applicability and/or use of the findings Discuss the scientific importance use of the findings Discuss the future use of the findings

Note: Adapted from the Standards for the Reporting of Diagnostic Accuracy studies checklist. Each feature assessed could gain 1 point, or a part thereof if the only part of the data was reported up to a total score of 25.

Abbreviations: MRI, magnetic resonance imaging; SVD, small vessel disease.

Reporting subject data

Reporting of SVD risk factors and conditions affecting subjects in life was variable. Twenty-one of the 38 papers reported individual subject data for each subject with SVD [32,33,37–42,44–49,51–53,55,62,66,69], 13 of which included SVD risk factors (Figures 2 and 3) [33,37,38,41,44–48,52,53,62,66]. SVD risk factors were not reported in some or all of the subjects in 13 of the 38 studies (Figures 2 and 3) [34,40,42,49,54,55,58–61,67–69], mostly community-based cohorts of older subjects with dementia or other neurodegenerative conditions and controls, or unselected subjects. The presence of hypertension, stroke, ischaemic heart disease and conditions predisposing to thrombus formation was reported most often (Figure 3).

Radiological–histological correlation

A range of methods were used to compare imaging and histological lesions. Attempts to make the lesion comparisons more precise involved using computer software to guide brain cutting, using topographical features to select lesions [51], or software aligning the MR image to histology then overlaying the images to identify areas of interest [62]. One study described specifically using only samples where the precise matching sulcal pattern could be identified [57]. Ferrous [46] and plastic [58] markers were also used to increase the precision of cutting planes.

Most frequently, MRI was used to guide sampling for histological examination [43–45,52,53,61,64,66,67,70]. Where the whole brain was scanned, radiologists were sometimes present at the brain cut [32,49], with additional brain slice scans after cutting in one paper [48]. Brain slices were imaged then sampled in some studies [47,56,59,64,67], three also described measures to slice the brain at the same thickness as the MR slice [44,46,49]. The whole brain was scanned and assessed with routine predefined samples taken for histology in five studies [34,50,54,58,65]. One study imaged hemispheres then carried out whole hemispheric histological sampling [55], another imaged hemispheres and chose MR regions of interest corresponding to the histological samples taken [69], and one scanned individual histological tissue blocks that were processed afterwards [40]. No description of the correlation technique was given in one paper [68], whereas

TABLE 3 Summary of papers studying non-haemorrhagic SVD

Paper (lead author, year)	Cohort origin	Number of cases with SVD (total scanned)	Number of female subjects in those with SVD (in total)	Mean age (range) (unless otherwise stated)	Data collection	MRI field strength	Tissue scanned (medium)	Quality score
WML								
Awad (1986) [51]	Arizona, US	7 (7)	2 (2)	72 (61–84)	Not stated	1.5T	Whole brain (2 fresh in isotonic saline, 8 fixed in formaldehyde solution)	16.75
Braffman (1988) [32]	Philadelphia, US	X Duplicated subjects used in Braffman 1988 (33)	X	67 (60–78)	Not stated	1.5T	Whole brain (water)	10.50
Marshall (1988) [54]	California, US	6 (18)	– (–)	>60 (–)	Not stated	0.35T	Whole brain (–)	7.75
Revesz (1989) [47]	UK	4 (6)	2 (–)	52 (40–68)	Retrospective	0.5T	Slices (–)	12.00
Fazekas (1991) [52]	Austria	4 (4)	0 (0)	59 (52–63)	Not stated	1.5T	Whole brain (–)	11.00
Grafton (1991) [46]	Seattle, US	5 (7)	– (–)	77 (69–88)	Retrospective	0.5T	Whole brain (air)	15.75
Van Swieten (1991) [50]	Netherlands	10 (40)	– (19)	76 (–)	Retrospective	1.5T	Whole brain (formalin)	12.50
Chimowitz (1992) [45]	Ohio, US	7 (7)	4 (4)	68 (64–74)	Retrospective	1.5T	Whole brain (water)	12.25
Munoz (1993) [57]	Canada	13 (15)	– (11)	69 (47–87)	Not stated	1.5T	Whole brain (air)	14.00
Scarpelli (1994) [48]	Italy	17 (21)	7 (9)	74 (65–94)	Retrospective	1T	Whole brain, slices scanned if MR lesions but macroscopically normal (water)	15.25
Scheltens (1995) [49]	Netherlands	– (15)	– (9)	73 (60–83)	Retrospective	0.6T	Whole brain (–)	15.75
Fazekas (1999) [53]	Austria	9 (11)	4 (5)	72 (45–90)	Not stated	1.5T	Slices (–)	17.00
Smith (2000) [34]	Kentucky, US	X Can't be sure subjects not same as those in Smith 2000 (63)	X	– (83–99)	Prospective	–	Whole brain (–)	15.50
Smith (2000) [65]	Kentucky, US	52 (54)	52 (54)	89 (SD 4.8)	Prospective	–	– (–)	13.50
Bronge (2002) [44]	Sweden	6 (6)	3 (3)	87 (81–101)	Retrospective	1.5T	Whole brain (air)	13.25

(Continues)

TABLE 3 (Continued)

Paper (lead author, year)	Cohort origin	Number of cases with SVD (total scanned)	Number of female subjects in those with SVD (in total)	Mean age (range) (unless otherwise stated)	Data collection	MRI field strength	Tissue scanned (medium)	Quality score
Fernando (2004) [59]	UK CFAS	X Can't be sure subjects not same as those in Fernando 2006 (58)	X	85 (median) (70–97)	Prospective	1T	Slices (in plastic bag)	19.00
Moody (2004) [56]	N Carolina, US	12 (21)	6 (9)	72 (58–90)	Not stated	1.5T	Slices (between cooled plastic sheets)	14.25
Fernando (2006) [60]	UK CFAS	– (456)[a]	– (–)	Over 77% >80 years (–)	Prospective	1T	Slices (sealed in polythene)	12.75
Matsusue (2006) [66]	Japan	– (–)	– (–)	– (–)	None given	1.5T	Whole brain (–)	6.00
Simpson (2007) [63]	UK CFAS	X Can't be sure subjects not same as those in Fernando 2006 (58)	X	Median ages of cohorts range 84–87 (68–95)	Prospective	1T	Slices (plastic bag)	16.00
Simpson (2007) [64]	UK CFAS	X Can't be sure subjects not same as those in Fernando 2006 (58)	X	Median ages of cohorts range 80–87 (68–100)	Prospective	1T	Slices (plastic bag)	14.50
Young (2008) [66]	Australia	20 (20)	8 (8)	76 (61–94)	Prospective	3T	Whole brain (agar)	18.50
Polvikoski (2010) [58]	Finland	132 (132)	114 (114)	91[b] (85–105)	Not stated	1.5T	Whole brain (0.1mM MnCl2)	16.00
Auriel (2011) [43]	Hungary	–	–	64 (–)	Retrospective	1.5T	Whole brain (–) Ex vivo scanning only of brains with poor quality in vivo MRI and control cases	15.50
Murray (2012) [62]	Florida, US	– (4)	– (2)	85 (74–90)	Prospective	3T	Hemisphere (distilled water)	14.75
McAleese (2013) [55]	UK NBTR	– (40)	– (25)	83 (68–98)	Not stated	4.7T	Hemisphere (air)	14.25
Hainsworth (2017) [61]	UK CFAS	X Can't be sure subjects not same as those in Fernando 2006 (58)	X	86 (SD 7.7)	Prospective	1T	Slices (in polythene bag)	14.75
Van Veluw (2019) [69]	Massachusetts, US	9 (11)	2 (3)	75 (64–95)	Not stated	3T	Hemisphere (plastic bag filled with periodate-lysine-paraformaldehyde fixative)	18.75

(Continues)

TABLE 3 (Continued)

Paper (lead author, year)	Cohort origin	Number of cases with SVD (total scanned)	Number of female subjects in those with SVD (in total)	Mean age (range) (unless otherwise stated)	Data collection	MRI field strength	Tissue scanned (medium)	Quality score
Waller (2019) [67]	UK CFAS	X Can't be sure subjects not same as those in Fernando 2006 (58)	X	— (71–101)	Prospective	1T	Slices (in plastic bag)	15
PVS and lacunes								
Bokura (1998) [41]	Japan	— (12)	— (2)	76 (61–90)	Retrospective	1.5T	Whole brain (—)	12.25
Braffman (1998) [33]	Philidelphia, US	9 (36)	5 (18)	66 (37–78)	Not stated	1.5T	Whole brain (water with very dilute amount of formalin)	10.50
Van veluw (2016) [42]	Netherlands	1 (1) 4 additional cases appear to be used in van Veluw 2015 (37)	1 (1)	76 (68–84)	Retrospective	7T	Slices (10% formalin)	14.50
Microinfarcts								
Van Veluw (2013) [38]	Netherlands	X Can't be sure cases not used in van Swieten 1991 (48)	X	74 (64–87)	Retrospective	7T	Slices (formalin)	16.75
De Reuck (2014) [35]	France, Belgium	— (175)	— (76)	Median ages of cohorts range 65–84 (—)	Not stated	7T	Slices (physiological saline)	16.00
De Reuck (2015) [36]	France, Belgium	X Can't be sure cases not used in De Reuck 2014 (33)	X	Median ages of cohorts range 65–82 (—)	Not stated	7T	Slices (salt-free water)	14.50
Van Veluw (2015) [39]	Netherlands	9 (11)	6 (8)	72 (65–88)	Retrospective	7T	Slices (10% formalin)	16.75
Van Veluw (2016) [37]	Massachusetts, US	X Can't be sure cases not used in van Veluw 2019 (67)	X	85 (77–93)	Retrospective	7T	Slices (10% formalin)	17.25
Niwa (2017) [40]	Japan	10 (16)	6 (8)	82 (62–98)	Not stated	3T	Tissue blocks (water at 37°C)	13.5

Abbreviations: —, Information unknown; CFAS, Cognitive Function and Aging Study; MRI, magnetic resonance imaging; NBTR, National Brain Tissue Resource; SD, standard deviation; SVD, small vessel disease; T, Tesla; UK, United Kingdom; US, United States; WML, white matter lesion; X, Subjects not clearly unique from different study from same group/cohort.

[a]Numbers not clear in paper, minimum number likely included.

[b]Precise numbers not stated in paper, calculated from means provided.

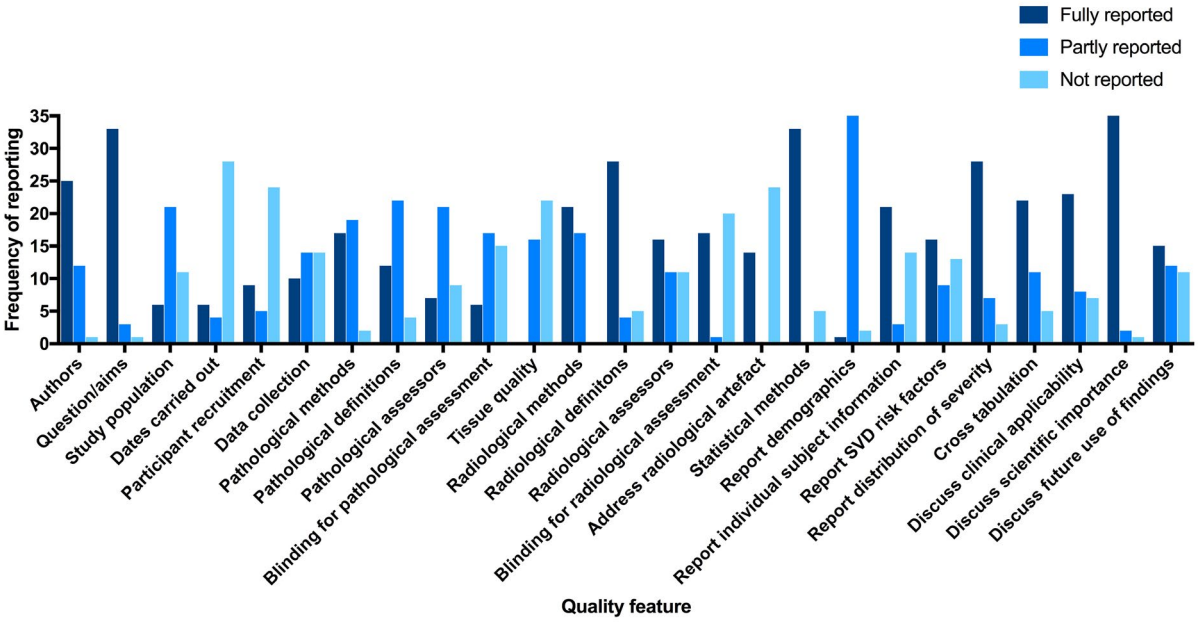

FIGURE 2 Bar chart showing how often the features used to measure study quality (detailed in Table 3) were reported in the studies included. Bars indicate the number of papers reporting each feature. The number that reported and fully met the criteria in Table 3 (dark blue), partly met the criteria (middle blue) or did not report that feature (light blue)

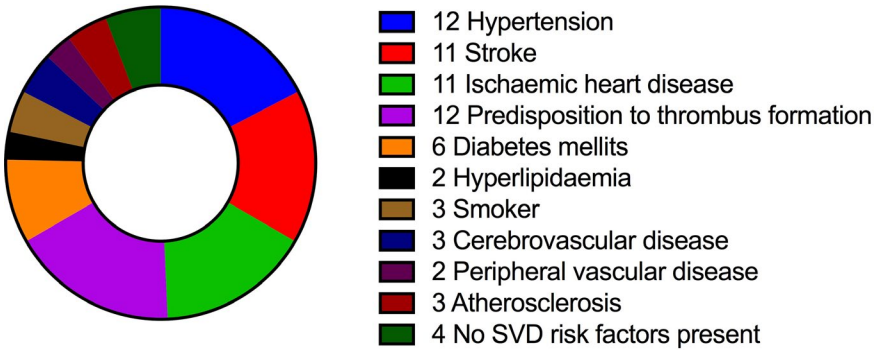

FIGURE 3 SVD risk factors and associated clinical diagnoses for individual subjects were reported in only 13 of the papers in this study. Some papers reported more than one risk factor, some only one. This figure shows the frequency with which each risk factor was reported. Hypertension, a predisposition to thrombus formation, stroke and ischaemic heart disease were reported most often. The block indicating hypertension begins at 12 o'clock and proceeds clockwise in the same order indicated in the key. SVD, small vessel disease

one reflected that 10 mm MR slices were not comparable to the micron scale of histological slices [47].

One paper that included both in vivo and ex vivo imaging without clarifying which results were obtained from which method [43] was included as the imaging was of high quality. One subject in one paper underwent imaging 11 days prior to death and although imaging could not be undertaken post-mortem, this case was included in the results without distinction from those with ex vivo MRI [51]. We felt this paper provided unique and important data and should be included within our review despite this. One paper reported two studies that were undertaken, but only the second study used post-mortem MRI and is included here [66].

MR methods

Ex vivo scanning

All used MRI, most at 1.5 Tesla (T) [32,33,41,43–45,50–53,56–58,68], with the majority scanning the whole brain [32–34,41,43–46,48–52,54,57,58,66,68]. One study used a diffusion-weighted sequence at 3T [69]. Several scanning mediums were used, including water [32,33,36,40,45,48,62], formalin [37–39,42,50,51], sealing the tissue in plastic [59–61,63,64,67] or placing between plastic sheets [56]. However, most studies did not state which scanning medium was used [34,41,43,47,49,52–54,65,68]. Tissue was scanned in air in four papers

[44,46,55,57], but some specifically avoided air due to artefact. Eleven studies took measures to avoid introducing MR artefact, usually by restricting tissue movement [35,36,66,69] (e.g. by wrapping in cling film [59,63,64,67]), or artefact due to air bubbles [38,39], by running a hand over the tissue [62], shaking the tissue [37], tilting to eliminate air from the ventricles [45] or vacuum sealing [69]. One study tested a variety of methods to reduce artefact, concluding water at 37°C was optimal and that embedding in agar, extended washing to remove formalin and removing the pia had no effect [40].

Establishing ex vivo MR parameters

One brain was scanned ante-mortem and post-mortem after fixation, and the same areas of hyperintensity were identified without obvious differences [54]. Two post-mortem brains scanned before and after fixation had identical WML appearances [51]. Three studies used clinical scanning protocols at post-mortem [40,45,52] and some described using optimised sequences, but without giving details [37,39,47,59–61,63,64,67]. T2-weighted sequences were said to be best for visualising WML ex vivo [52], whereas nine studies performed ex vivo fluid-attenuated inversion recovery (FLAIR) [38,39,43,46,47,50,60], two of which described protocol optimisation [62,66].

One study found a diluted formalin/water scanning medium was hyperintense on short TR sequences, compared to hypointense cerebrospinal fluid [33] and another stated that changes in signal intensity due to fixation made identification of lacunar infarcts difficult [53]. Only one study described optimisation of a T1 sequence [38].

In vivo imaging

A total of 105 subjects in five papers primarily studying WML had in vivo MRI available [32,43,51–53], of which at least 17 subjects also underwent ex vivo MRI and 15 additionally had in vivo CT [32]. In two papers studying PVS and lacunes, nine subjects underwent in vivo MR imaging and 20 had in vivo CT [33,41]. In one paper studying microinfarcts, although 12 subjects had both in vivo and ex vivo MRI carried out, comparison of the microinfarcts was possible in only one subject [37].

Autopsy and histological methods

Post-mortem

The PMI was reported in 14 studies and ranged from <24 h [34,40,44,46,48,49,55,64,66,67,69] to 7 days [64]. Most studies had multiple cases, and PMIs varied considerably within each study. The most common method of fixation was to fix the whole brain in a variety of formalin solutions [32–39,41–52,54–63,65–69] although one study did not describe how the tissue was fixed [64]. The duration of tissue fixation ranged from slices in a formalin solution overnight [56] to slices formalin fixed for 12 years [47]. One study noted that the MR image quality was not affected by different fixation periods from 9 to 35 days [46] and when the time between death and scanning was controlled for statistically, it did not alter the results obtained by DTI in cases ranging from 27 to 498 days [69]. Assessment of post-mortem tissue quality using methods such as pH or RNA-integrity number measurement was not reported. Three papers commented on storage temperatures; one cooled brains after autopsy [56], one stored them at room temperature [34] and the third stored hemispheres at 4°C until the day before scanning when they were transferred to room temperature [69].

Macroscopic examination

Nineteen studies described macroscopic examination [32–35,41,44–52,54,57,58,62,65] including photography [32,33,47,51,54], brain weight [34,45,47–49,51,52,58,62,65] or describing some general aspect of macroscopic inspection [34,35,41,44,46,47,49–51,54,57,58,62,65].

Staining and special techniques

All papers described using special tinctorial or immunohistochemical staining to characterise tissue lesions. Haematoxylin and eosin was most often used for general tissue architecture [32,33,37–41,43,44,47–49,51,52,54,55,57–60,62–64,66,69] followed by myelin stains, particularly Luxol fast blue [34,38,39,41,43–48,51,52,54–56,59,60,62–64,69], glial stains [39,43,45,46,48,51,54,62–64,68,69,71] and a variety of neuronal, microglial, endothelial and amyloid stains. More recently, papers trying to assess specific mechanisms such as inflammation, hypoxia and BBB, have used a wider range of markers to assess the different pathways [54,59–61,63,64,66,67].

Pathological terminology and definitions

Pathological lesions were less well defined than MRI lesions (Figure 2). The histopathological definitions and terminology used were variable between papers (see Table S1 for full library of terms), so we have had to apply a degree of interpretation, aiming to group lesions as objectively as possible by their morphological appearance and staining characteristics rather than the presumed underlying cause.

A range of histological findings were described corresponding to radiological SVD (Figure 4A), most often a variety of WM changes including myelin and axon pallor (Figure 5), microscopic 'abnormalities', rarefaction and degeneration. Radiological WMH corresponded to several histological appearances (Figure 4B), typically more than one. In particular, the range of terminology describing vascular pathology of radiological WMH was wide and often poorly defined (Figure 4C).

Perivascular spaces, also known as Virchow–Robin spaces, (Figure 6) were defined in two of the three papers studying them

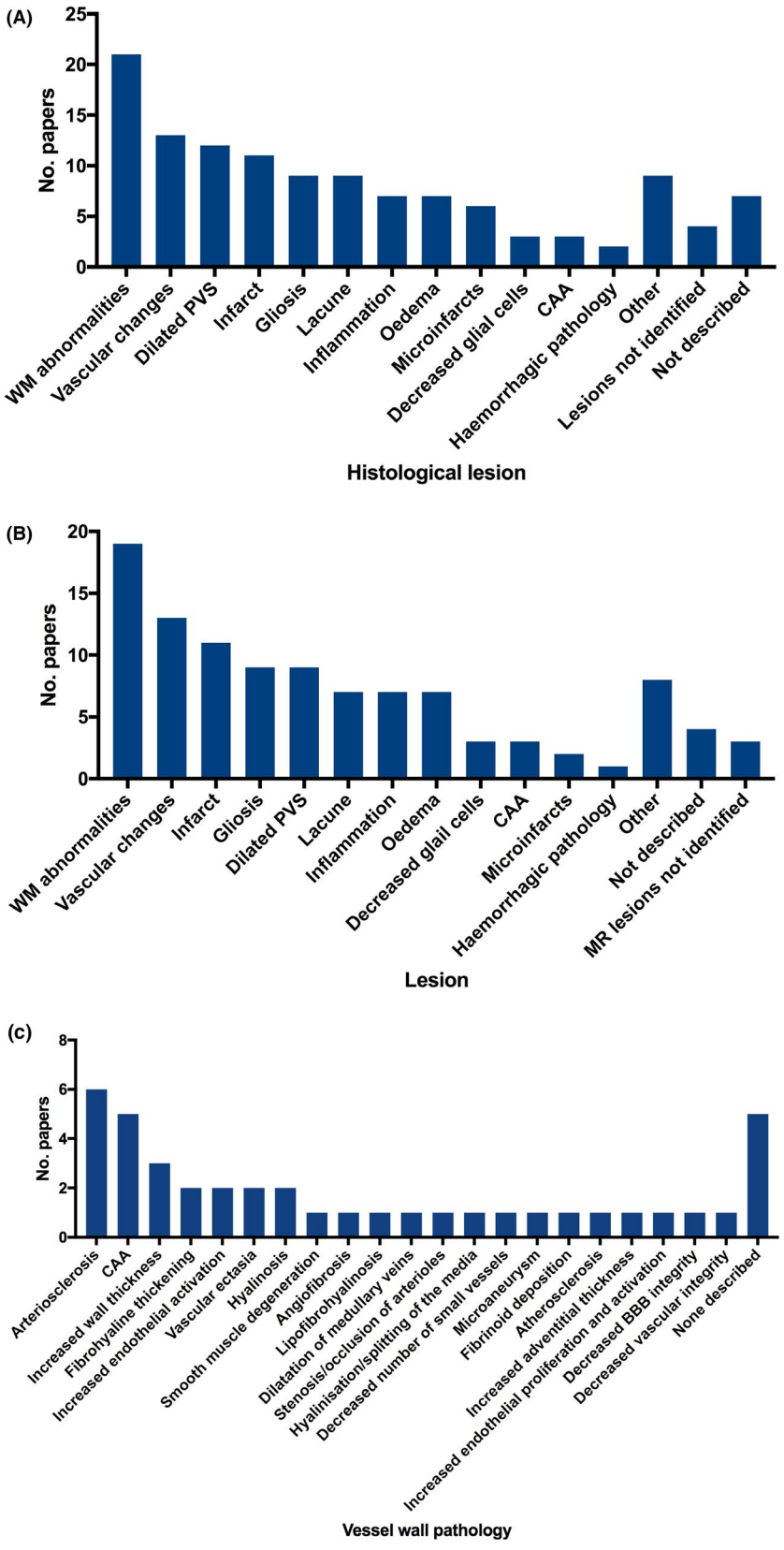

FIGURE 4 Histological lesions and terminology. For clarity and to avoid many small groups, some headings contain terms used to describe similar pathologies, some of which were not specifically defined and reflect the variation of terminology summarised in Table S1, for example 'WM abnormalities' include rarefaction, myelin pallor, demyelination, abnormal myelin sheaths, degenerate myelin, decreased axonal staining, decreased axons and Luxol fast blue lesions. BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; PVS, perivascular space; WM, white matter. (A) Histological lesions described microscopically corresponding with all radiological small vessel disease lesions. (B) Histological lesions described microscopically corresponding with radiological WM lesions only. (C) Histological terminology used to describe the spectrum of vessel wall changes seen in radiological WM lesions

specifically as the subarachnoid space around small vessels in the brain excluding capillaries [33,41]. Enlarged PVS were described as a marker of SVD and defined as spaces filled with interstitial fluid surrounding these vessels [42]. *État pre-criblé* was described as thin, pale and sinuous myelin in surrounding parenchyma, without PVS dilation. Subsequent rarefaction and disintegration of the perivascular parenchyma [33] resulting in *état criblé* in which PVS are dilated. Associated surrounding changes may be present,

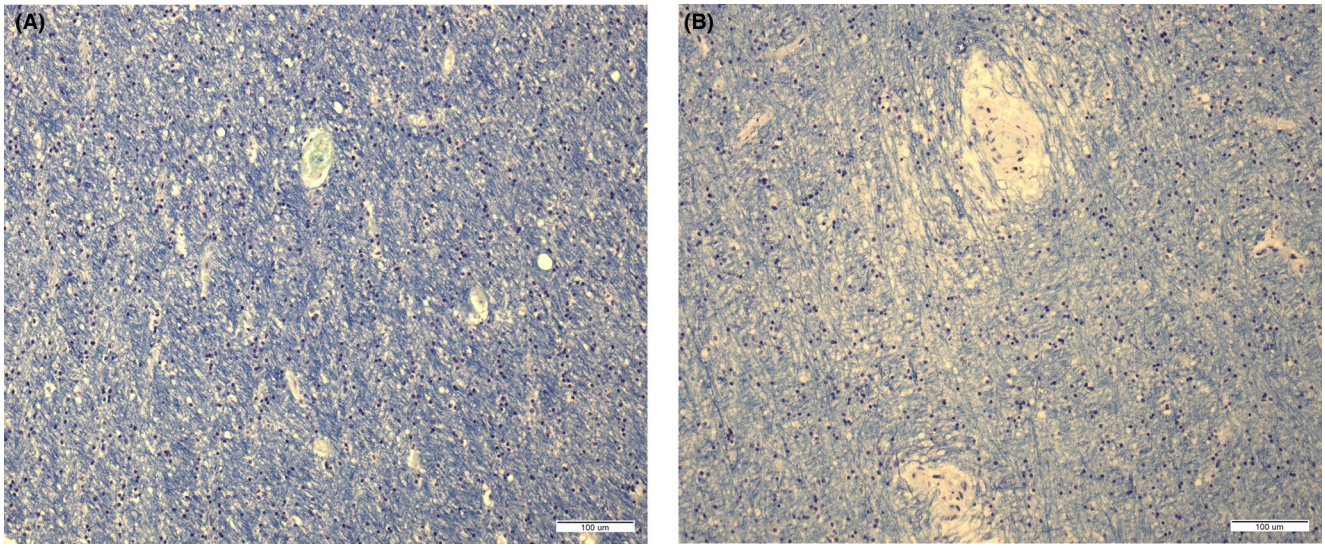

FIGURE 5 (A) Normal central white matter showing uniform myelin staining (LFB ×100). (B) Central white matter from a case with severe small vessel disease, showing pallor and fine vacuolation between axon sheaths (LFB ×100). LFB, Luxol fast blue

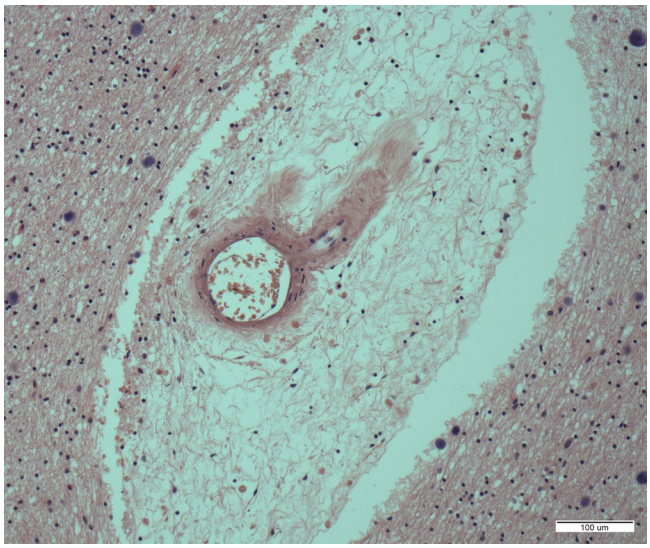

FIGURE 6 An enlarged perivascular space from the region of the central white matter. There is a central vessel with marked expansion and fibrillation of the surrounding perivascular space (haematoxylin and eosin ×100)

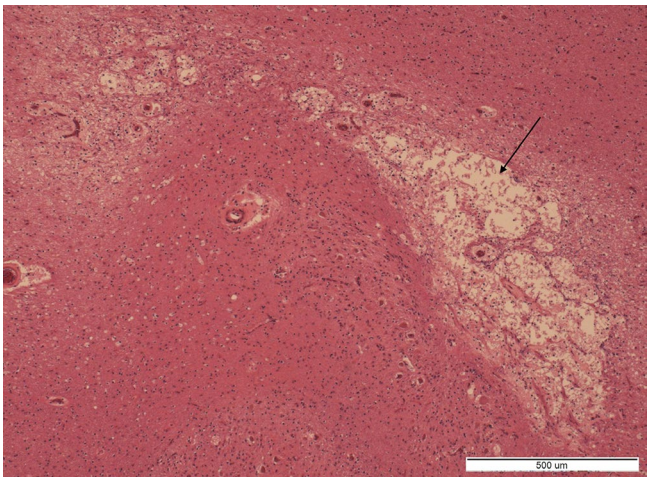

FIGURE 7 A lacunar infarct (arrow) in the internal capsule with gliosis and cystic degeneration, measuring <10 mm in maximum diameter (haematoxylin and eosin ×40)

including a narrow border of fibrillary gliosis or demyelination [33].

Lacunes (Figure 7) were 'a lesion surrounded by gliosis and myelin loss' histologically [41] or more mechanistically as 'infarctions caused by perforating branch occlusion' in white and deep grey matter [33]. They were also called penetrating branch occlusions and lacunar infarcts. In these studies, size was not a criterion [33]. Recent lacunar infarcts showed liquefactive necrosis [33] and when older form an irregular cavity with fibrillary connective tissue and macrophages, which decrease with time [33]. *État lacunaire* described the presence of multiple lacunar infarcts [33] and giant lacunae were defined as >1 cm diameter [33].

Six papers studied cortical microinfarcts (Figure 8) using a variety of overlapping definitions, but these papers came from only three groups. From defined areas of tissue pallor [37,39] to 'ischaemic necrosis in the territory of a single cortical penetrating vessel' [35], ischaemic lesions with cell death or necrosis, sometimes with gliosis, haemosiderin-containing macrophages and cavitation [38,39] or well-defined ischaemia with cell death, necrosis and cavitation [40]. One differentiated acute microinfarcts with tissue loss and gliosis from old microinfarcts with ischaemic or shrunken neurons [37], but the size was not defined in advance. In the others, sizes were described as between 50 μm and 2 mm, depending on the size

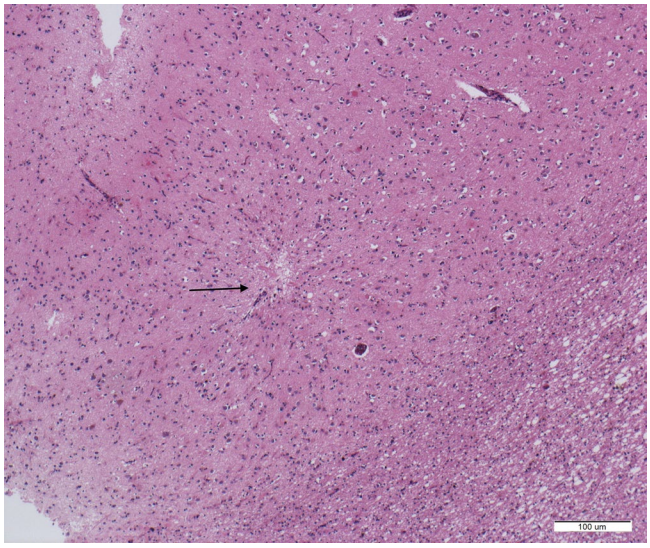

FIGURE 8 A cortical microinfarct (arrow) with localised tissue loss and reactive gliosis, the lesion being found on microscopic examination but not visible to the naked eye examination (haematoxylin and eosin ×100)

of the involved vessel [35], or from 50 μm to a few mm [38,39], but also as almost visible on gross examination [35,36,39] or microscopic [38]. One did not define or describe the histological appearance [36].

Papers studying WMH

Macroscopic comparisons

Where MR-defined WMH were compared with macroscopic appearances, tissue softening, pallor and loss including infarcts or spaces consistent with lacunes or PVS [32,45,47,48,51,54] were described most often. However, there were often no obvious macroscopic changes [46,48,49,52] or only subtle discolouration [47,51]. Macroscopic lesions in one study were on average 54% larger than on MRI [44] and were more extensive in another [57]. A separate study found differences between areas of high signal intensity (discolouration and dilated PVS) and areas of relatively lower (but still increased) MR signal change, which could not be identified [62]. Naked eye examination of histological slides stained for myelin or axons described pallor in areas of radiological WMH [50,57].

Precise microscopic comparisons

Twelve papers attempted to make direct comparisons between imaging WMH and corresponding histological lesions, and some described pathology in specific locations. WMH in the centrum semiovale showed variable white matter pathology. WMH in seven brains (five with bilateral discrete WMH, two with 'diffuse change') revealed dilated PVS containing fluid and macrophages, myelin and axonal pallor and gliosis [46]. Thirty-three extensive WML corresponded with poorly defined areas of myelin pallor that appeared larger on histology. They contained axonal swellings and loss, and involved subcortical U-fibres when severe with WM vacuolation ('spongiosis'), decreased oligodendroglial numbers and dilated PVS throughout. Twenty-one per cent (n = 7) of the extensive WML also contained focal perivascular or scattered diffuse vacuolation. One WML was close to a small infarct and one contained a small haemorrhage [57]. WML corresponded to myelin rarefaction in five brains (three in the centrum semiovale, two periventricular). All five brains had moderate-severe lipofibrohyalinosis and one had diffuse WM oedema in the centrum semiovale [53]. Seven WML corresponded with histological infarction; one of which had surrounding gliosis correlating with the WML, one was recent with early cavitation, macrophages and surrounding gliosis [32] and two in the left frontal WM were old with a 1 cm cavity and 3 cm of surrounding gliosis. An unspecified number of small intermediate and old infarcts with surrounding isomorphic gliosis were also found in frontal, mid-coronal and occipital WM [54]. One cerebellar WMH corresponded with a 3 cm infarct histologically [54]. 'Isomorphic gliosis' and IgG in astrocytes extended up to 3 cm from old infarcts (showing cavitation and minimal gliosis, some with demyelination) and the ventricles [54]. Pontine WMH revealed severe gliosis and axonal and myelin loss [47]. Periventricular WMH contained myelin pallor, dilated PVS, subependymal gliosis and increased extracellular spaces accompanying disrupted ependymal [68].

The locations of some lesions and pathologies were not specified. One study sampled 27 radiological WMH from 16 brains (centrum semiovale in two brains, adjacent to the frontal horns of the lateral ventricles in two, optic radiations in five and basal ganglia in three; the number of samples per brain/area is not described). 100% of WMH sampled (n = 27) contained at least one severe pathology of arteriolar sclerosis, vascular ectasia or dilated PVS [51], 85% (n = 23) had two severe changes. Fifty-nine per cent (n = 16) also showed subependymal gliosis, associated with myelin pallor, axonal loss, dilated PVS, vascular ectasia and arteriolosclerosis. In 15 control areas sampled, 27% (n = 4) had one severe pathology and 7% (n = 1) had two severe changes [51]. In another study, 141 deep subcortical WMH showed severe myelin pallor and damage [59]. Of nine larger (not punctate) subcortical WMHs, 78% (n = 7) showed prominent myelin pallor and PVS with parenchymal oedema, 67% had gliosis (n = 6), 44% macrophage infiltration (n = 4) and 33% arteriosclerosis (n = 3). Twenty-six per cent (n = 5) of punctate WMH showed periarteriolar demyelination often surrounding enlarged PVS and 16% (n = 3) had perivenous demyelination. At least one was in the external capsule [52]. In another paper, deep and subcortical WML, both punctate and confluent, corresponded with histological myelin pallor and dilated PVS [68].

One paper was difficult to interpret but seemed to identify six infarcts, four old and two recent [48]. Two small areas in the corona radiata showed recent infarction with macrophages and inflammation

surrounded by degenerate myelin, and one cystic area in the internal capsule corresponded to a dilated PVS containing an ectatic, sclerotic artery and macrophages with surrounding fibrous gliosis [48].

In surrounding, radiologically non-lesional tissue, there were eight areas of enlarged PVS, five parenchymal oedema and four of inflammation [45], and two areas of histological gliosis/non-cavitated minute infarction were adjacent to areas of fibre loss with fibrillary necrosis and cavitated, gliotic infarcts [32]. Eleven per cent (n = 10) of control samples contained intermediate necrotic lesions with surrounding gliosis [54]. In tissue adjacent to six punctate WML, 50% (n = 3) contained dilated PVS, 33% (n = 2) gliosis and 17% (n = 1) each with arteriosclerosis and myelin pallor [45].

Binswanger's disease described radiologically as 'irregularly distributed WML relatively sparing the temporal lobe' showed histological moderate rarefaction with loss of myelin, axons and oligodendrocytes, and mild gliosis and arteriosclerosis [68].

Radiological DTI abnormalities replicated those seen in vivo and were associated with the presence of microinfarcts in posterior white matter. Abnormal fractional anisotropy was more sensitive to axonal loss, whereas increased mean diffusivity reflected myelin loss in CAA [69].

An assortment of other histological lesions appeared as radiological WML. Several so-called lacunae were identified: one with gliosis and myelin pallor surrounding 2 mm central area of necrosis [51]; one in the temporo-parieto-occipital deep WM with dense gliosis surrounding a cystic area [47]; two WMH in the globus pallidus and putamen corresponded to two lacunar infarcts with the same size on imaging and histology [54]; a poorly circumscribed, irregular WML with a halo of signal intensity was a poorly defined cystic cavity with surrounding mild gliosis [68]; a large circumscribed area of low signal in the putamen showed an empty cyst with previous haemorrhage [47] and multiple lacunae were found in the basal ganglia of three brains and the thalamus in two brains [53]. A circumscribed linear WMH smaller than 3 mm without surrounding signal change was a dilated PVS [68]; 88% (n = 15) of punctate centrum semiovale WMH contained dilated PVS on microscopy, 6% (n = 1) had small infarcts and CAA, whereas no histological abnormality was found in 6% (n = 1) [57]. Punctate WML additionally represented defined areas of demyelination, two subcortical ganglion cell heterotopias, one periarteriolar fibrosis and one perivenous oedema [52]; one case with telangiectasia [51] and two areas of demyelination, one cyst and one congenital ventricular diverticulum [32].

Histological cribriform changes, with a sieve-like pattern of 'holes' of varying sizes in the basal ganglia (*status cribrosum*) were seen in eight subjects: 38% (n = 3) in the presence of radiological lacunes, 25% (n = 2) with a single radiological lacune but without any MRI correlate in 38% (n = 3). This could reflect the low resolution of the MRI with a 1T field strength and 5 mm slice thickness [53].

There were a number of post-mortem imaging-histology mismatches. Radiological lesions not identified on histology included 36 WMH [32,52,59] plus multiple lacunes in the centrum semiovale, brainstem and cerebellum [53]. Histology revealed lesions not seen on imaging: 37 deep subcortical WM areas with moderate myelin loss and endothelial activation [59], three infarcts [32,48], two basal ganglia lacunes plus one white matter infarct and two small old cortical infarcts, with cribriform change in the cerebellum, basal ganglia and pons [53].

Vascular pathology

A range of vasculopathies were described in MRI WML (Figure 4C) and were often associated with other lesions but not correlated to the other changes. Atherosclerosis was common in periventricular lesions, with vacuolation and gliosis in neurologically normal cases in one study [48]. WML in four subjects contained lipofibrohyalinosis and CAA [53], two subjects additionally showing patchy, rarefied myelin. Lipofibrohyalinosis and CAA were also seen, however, in subjects without MRI WMH. Differing severities of angiofibrosis, hyalinosis and arteriosclerosis were present in 83% (n = 5) of six brains in another study, the remaining brain contained angiofibrosis and arteriosclerosis only [52].

Six punctate WMH examined in deep grey or white matter all showed enlarged PVS and perivascular gliosis. Two thirds of these WMH contained vascular ectasia, one third had perivascular inflammation and half arteriosclerosis [45]. Eight linear periventricular WMH, <2 mm thick, all contained prominent subependymal gliosis [45] and six focal WMH (<5 mm) at the poles of the lateral ventricles showed myelin pallor with arteriosclerosis and gliosis. Two thirds of the focal WMH had enlarged PVS, and one each had adjacent arteriolosclerosis, oedema and inflammation [45].

In vivo imaging in WML

Fazekas et al. noted many small WML (<5 mm diameter) in their study that would not have been identified post-mortem without knowledge of in vivo MR [52]. In vivo MR also appeared superior at detecting hypointensities [53]. In vivo CT did not identify a 4 × 4 mm area of gliosis/infarction, two areas of demyelination and one cyst measuring 6 × 6 mm which were subsequently seen on ex vivo MRI [32].

Non-precise WML comparisons

Deep subcortical WML showed a range of non-specific changes, particularly myelin pallor, vacuolation, decreased cellularity and dilated PVS [45,46,57,59,63,68], with more vasculopathies, including arteriolosclerosis, compared to periventricular WML [45]. Periventricular WML were associated with disruption of the ependymal [60,63], abnormalities in myelin, axons and astroglia [46,62,63], and sometimes with increased subependymal gliosis [45,68]. Overall, WML were larger on MRI than histology [41,54], usually of the order of about 25% with gliosis contributing to the MR appearance [32,54,68],

Some histological studies suggested roles for inflammation, BBB dysfunction and hypoxia in both periventricular and deep subcortical WML [60,62–64,66].

Radiologically normal-appearing white matter (NAWM) in subjects with WML was studied in some papers. It was histologically abnormal immediately adjacent to lesions [44,45,59], where it may represent a transitional zone, but also distant to lesions [64]. However, specific distances from WML, or graded changes as the distance increased, were not addressed. Suggested mechanisms included a global underlying pathology, possibly involving endothelial activation and inflammation. White matter in subjects without WML appeared normal with strong myelin staining in several studies [44,54,59]. Microglial staining characteristics and morphology differed between deep subcortical WML, NAWM and controls [67].

WML summary

- Macroscopic changes of WML include discolouration and softening but often no lesion was visible.
- Location of lesions was frequently not described; descriptions were sometimes difficult to interpret and overall difficult to summarise and compare due to differences in terminology and reporting.
- Location of lesions was most often described in the centrum semiovale.
- Microscopy of radiological WML commonly included myelin pallor, oedema and PVS dilation (Figure 5), as well as areas of tissue infarction and cavitation. Vascular pathology and inflammation were also seen.
- Gliosis contributes to hyperintensity on post-mortem MRI.
- Few studies have made precise comparisons of the gradation of histology from lesional to normal appearing tissue, and of radiologically NAWM in lesional brains.

Papers studying dilated PVS and lacunes

Three studies specifically reported dilated PVS and lacunes [33,41,42], two of which compared lesions identified on 1.5T MR with histology, on morphology and size [33,41]. Macroscopic examination confirmed the morphology seen on MR imaging [33].

Precise microscopic comparisons

At least five radiologically identified lacunes corresponded to microscopic cavities with surrounding gliosis and axon loss [47,48,68]; two also had perilesional macrophages and lymphocytes with neovascularisation [48]. Using a 1.5T scanner, one study described the hyperintense halo on MR corresponding with surrounding, partial myelin and axon loss, and gliosis [68].

Vascular pathology

Microscopic vascular wall pathology was not described.

Location

Lacunar infarcts and PVS were both more common in the basal ganglia and thalamus. Eighty-two lacunar infarcts were studied in total: 47 in the basal ganglia and thalamus, 24 in the white matter and nine in the posterior fossa [32,33,41,48,53,54]. Sixty-seven PVS were identified in one paper, 58 within the basal ganglia [41]; a second paper found four areas of dilated PVS in the putamen and white matter [33].

Size and morphology

Studies that compared size and morphology used 1.5T and a 5 mm slice thickness [33,41] or 0.35T and 0.95 mm resolution [54]. Lacunes were consistently larger than 2 mm in their greatest dimension on both MRI and histology [33,41], and were largest in the deep grey matter (3 × 1 mm to 14 × 13 mm), followed by posterior fossa (3 × 1 mm to 5 × 3 mm), being smallest in the white matter (2 × 2 mm to 4 × 2 mm) [33,54]. Their dimensions were the same on histology and ex vivo MRI [54] and they were most commonly wedge-shaped, but this was variable with slit-like, round and ovoid morphology also seen [33,41]. PVS were significantly smaller than lacunes in all areas studied except in the most caudal region of the basal ganglia [41]. PVS were predominantly round or linear in shape and <2 × 2 mm on MRI without perilesional signal change [68].

In vivo imaging

In vivo neuroimaging was performed in 26 subjects; 36 MRI lesions were identified and confirmed on pathology in six subjects [41]. In vivo CT identified all six histological lacunar infarcts in the basal ganglia and one of five in the WM, confirming their morphology, but did not identify any in the brainstem or areas of status cribrosum [33].

Dilated PVS and lacunes summary

- Five radiological lacunes were histological cavitated lesions (Figure 7).
- Lacunar infarcts and PVS were both more common in the basal ganglia and thalamus.
- Radiological lacunes were sometimes surrounded by signal change and were larger than 2 mm.
- Dilated PVS on MRI were smaller than lacunes (<2 × 2 mm) without perilesional signal change.

MRI-histopathological correlations on microinfarcts

A total of 570 microinfarcts were identified on MRI in 202 subjects, 69% (*n* = 396) of these from a single paper (we have calculated this figure from subject numbers and group means) [35]. The number of microinfarcts per subject ranged from 0 to 72. Sixty-seven per cent (*n* = 381) were found on histology. Two papers identified 86% (*n* = 327) of these but compared mean numbers between neurodegenerative disease subgroups only [35,36]. Twenty-six were precisely matched to MR-identified microinfarcts in three papers [37–39]. In another, 49 microinfarcts were initially identified on histology, 35% of these (*n* = 17) were subsequently found on 3T MRI [40]. Those found were all over 2 mm in size, but some microinfarcts over 2 mm and all less than 1 mm could not be seen on 3T MRI.

Seven MRI-identified microinfarcts were searched for on histology but not identified, and one was described as an area of rarefaction [39]. Fifty-six additional microinfarcts were identified on histology only [37–40]. They measured 0.6 mm diameter on average, below the current detection threshold for 7T scanners [39]. Nine histological microinfarcts were present in one small sample, none of which had been identified by ultra-high (100 μm^3) resolution MRI, although two identified at 300 μm^3 resolution were matched to histology with no additional microinfarcts being identified [37].

Precise microscopic comparisons

Microinfarct histology within the cortex was heterogenous [39]. Three studies identified 84 potential microinfarcts as hyperintense cortical lesions on T2 and FLAIR sequences [38] or any lesion smaller than 5 mm [39] or both [37]. Twenty-six were confirmed as different types of microinfarcts on histology. Fourteen with increased signal intensity on T2 and FLAIR sequences revealed histological chronic microinfarcts with pallor, gliosis and neuronal loss [37], sometimes with incomplete cavitation not visible on MRI [39]. Three were hyperintense on T2 and hypointense with a bright rim on FLAIR, histologically revealing fluid-filled cavities surrounded by gliosis. Three hypointense lesions on T2, FLAIR and T2* sequences showed histological haemosiderin-laden macrophages, gliosis and neuronal loss [39]. Six acute lesions showed red neurons and WM pallor [37], and one was hypo-isointense on T2 and FLAIR [39]. One study stated microinfarcts and PVS had similar appearances on MRI, but could be differentiated by their location, PVS being just below the corticomedullary junction [40].

Chronic lesions measured 1.2–2.5 mm [38], smaller than the single acute microinfarct measuring 4.4 mm. Sizes were not significantly different between MR and histology [37].

Location

Microinfarcts occur throughout the brain [72]. However, in the five studies included here, four specifically aimed to study intracortical microinfarcts and one studied them in the context of CAA, which predominantly affects the cortex. It is therefore not unexpected that all microinfarcts identified in these studies were intra-cortical. They were seen in all layers, often in the most superficial layer [35] where they sometimes caused a small surface retraction [39], or extended to two or more layers [38,39]. They were more commonly seen in parietal and frontal cortex [38] and appeared to cluster on MRI [37]. In both CAA and VaD, they were often superficial [35]. Cerebellar microinfarcts were more common in VaD, where they were also associated with leptomeningeal arteriosclerosis [36]. Detailed histological assessment of 12 radiological juxtacortical microinfarcts revealed eight PVS, one primary haemorrhage and one venous angioma; two lesions were not identified [39].

In vivo imaging

In vivo 1.5T MRI was examined retrospectively in one paper and no microinfarcts were visible [37]. Another study found 15 possible microinfarcts on in vivo 7T MRI; four were identified on corresponding in vivo 3T T1 and/or T2 sequences but ex vivo MRI and histology were not undertaken [38].

Non-precise microinfarct comparisons

A number of microinfarcts seen on MR imaging as small, well-defined hyperintensities on T2, not visible on T2* were compared but not described histologically in two studies [35,36]. More microinfarcts were identified in cases with neurodegenerative pathology and CAA when compared with non-neurodegenerative brains [36].

Microinfarcts summary

- Twenty-six histological lesions were precisely matched to MR-identified microinfarcts.
- Histological appearances were variable, most often (in 54%) revealing foci of chronic neuronal loss and gliosis; acute changes with red neurons and white matter pallor were seen in 23% (Figure 8).
- A significant number of microinfarcts identified on histology were too small to be seen on MRI up to 7T.

CAA

As stated, we excluded studies of only haemorrhagic pathology, which includes the bulk of reporting on CAA, a major cause of spontaneous intracerebral haemorrhage [73]. However, many studies did not describe subjects with amyloid and non-amyloid pathology separately and a number of lesions related to CAA were described within these studies, they are included here.

CAA and radiological WML

Most histological studies found no association between cortical or leptomeningeal CAA and radiological WML [43,45,49,54,56,57]. One study of WML found no CAA in thickened hyalinised vessels [54]. Cortical and leptomeningeal CAA correlated with increased levels of the hypoxia marker HIF-1α in deep subcortical WML only [60].

CAA and radiological PVS

One paper reported a significant positive relationship between severity of histological cortical CAA and of radiological juxtacortical dilated PVS [42].

CAA and microinfarcts

Intracortical microinfarcts, rather than juxtacortical and deep white matter infarcts, may be associated with severe CAA [35,74]. The number of the smallest superficial cortical microinfarcts was increased in Alzheimer's disease with CAA, and in VaD [35]. Seventy-two per cent of microinfarcts in one paper were associated with moderate to severe CAA; one-third of these were identified on ex vivo MRI. 48/48 cortical microinfarcts in subjects with CAA were associated with vascular abnormalities, 33 were close to amyloid-ß positive vessels and 15 to vessels showing 'double-barrelling' arteriopathy associated with CAA.

DISCUSSION

This review has highlighted the variability in methodology and reporting in radiological–pathological comparisons in sporadic human cerebral SVD. The earliest of these papers were published in the 1980s when MR resolution was much less sensitive than it is today, and SVD knowledge was much less refined. There has since been a consensus on neuroimaging terminology and techniques [1], used in subsequent papers [37,39,42]. However, pathological terminology and reporting remains variable [75], limiting the reproducibility and interrogation of findings [76] and making it difficult to identify and interpret relevant literature (Table S1). As such, we recognise that some relevant studies may have been overlooked in this systematic review. Lesions were often poorly defined histologically, and some histological changes with unknown significance overlooked, such as venous collagenosis and fibrinoid necrosis. In particular, the term 'infarct' is in common use histologically but the precise definition is lacking and, our results indicate, is inconsistent with the term used in vivo.

Tissue 'oedema' and PVS dilatation were frequently observed on histopathology in WMH; although these features have received less attention to date in the pathology literature than myelin loss, oedema and PVS dilation correspond with findings on in vivo MRI suggesting that WMH (and the perilesional penumbra) have increased tissue water and increased BBB leakage [77,78]. It also concurs with the reduction in WML seen in vivo at follow-up in some patients associated with reductions in brain tissue water [79]. Additionally, PVS dilation in subcortical tissues is associated with increased severity of WML and other features of SVD and may reflect impaired tissue fluid and waste clearance [80]. Widespread signal changes are seen in post-mortem brains with neurodegenerative pathology, such as altered T2 [81] and R2 (transverse relaxation rate) [82] in multiple areas including white matter and may be associated with mild cognitive decline. However histological correlation is needed in more studies to understand the pathological substrate of these appearances.

Alterations in normal appearing white matter adjacent to SVD lesions are seen [44,45,59] including specific axonal alterations in nodes of Ranvier and paranodal regions adjacent to lacunar infarcts [83], but no studies that we are aware of have addressed histological gradients of abnormality around lesions.

Some studies describe risk factors for SVD, but clinical risk factors are generally under-reported and the full association with radiological and pathological burden remains unclear [84]. Medical histories were usually collected retrospectively and therefore common vascular risk factors are likely to be under-recognised. Cardiovascular risk factors are the most strongly associated modifiable risk factors for SVD, and WML were the focus of most radiological–pathological correlation studies assessed in this review. However, it should be noted that cardiovascular risk factors explain only 2% of the variance in WMH on imaging [85], and other potentially modifiable risk factors current remain unknown.

The importance of radiological–histological comparisons is well recognised [86]. However, a significant proportion of lesions, particularly microinfarcts, microbleeds and microvessel pathologies remain undetected on neuroimaging at current clinical field strengths [37] and this is reflected in the range of field strengths and slice thicknesses used in these studies. Higher field strengths, for example 3T, reveal lesions for which we currently lack pathological comparative material and the technology required to accurately compare radiological and histological lesions.

Tissue storage and fixation times varied from overnight [56] to 12 years [47]. Although no formal quality assessments were made, no changes were reported that affected the ability to assess the tissue on post-mortem imaging or histology. Repeated and high field MRI examination of post-mortem tissue does not appear to compromise histological examination but the interpretation of post-mortem MR images should consider differences in the superficial and deep aspects of tissue that have been submerged in formalin [87,88].

There is significant radiological and pathological heterogeneity in SVD. Advances in understanding of the clinical consequences of SVD with ageing have come from imaged cohorts followed over a life course (such as the RUN DMC study [89] and Lothian Birth Cohort 1936 [90]), and the introduction of the STRIVE consensus standards for neuroimaging [1] has introduced a standardised approach

across neuroimaging SVD studies. Pathological studies now have to follow this established pathway. The number of direct radiological–pathological comparison studies to date are small, and of course, pathological studies are, by their nature, static. Radiological studies highlight the dynamic nature of SVD, and therefore the cohorts used to study SVD should be well-characterised clinical and radiological cohorts with brain donation programmes. Making precise comparisons is resource-intensive but possible [91]. Initiatives such as the Medical Research Council's UK Brain Bank Network [92] is helping to generate an accessible well-characterised brain tissue resource linked to detailed clinical and imaging data. Standardised histological approaches to assessing the contribution of SVD to an overall diagnosis of cognitive impairment have been published [2,23], and while the need to standardise the basic pathological protocols and descriptions of SVD has been recognised [11], to date no standardised consensus statements have been published. To maximise gain from the valuable brain bank resources, future studies must be of high quality, with subjects characterised as fully as possible in vivo, and standardised methods of tissue assessment (both radiologically and histologically), using standardised terminology and reporting.

Standardised methods for processing post-mortem tissue should address artefact, particularly as MRI field strengths continue to increase towards microscopic resolution [37]. These approaches need to account for post-mortem thrombi within vessels and air bubbles that can mimic small haemorrhagic lesions on ex vivo MRI [93], and the effects of heating during MRI on tissue quality and artefact. Brain tissue absorbs more radiofrequency than other tissue and in vivo mechanisms such as vasodilation, which usually dissipate heat [94], are absent. Tissue quality assessment is important as it reflects the potential for artefact, alters MR imaging properties [87] and is essential for further use of tissue, such as genetic assessment, a logical extension of these studies [95].

This review is limited as it does not include individual case studies and abstracts not written in English. It is potentially limited by the search strategy applied and publication bias. However, this is the nature of systematic reviews and we do not believe we have missed any significant publications comparing radiological and histological appearances of SVD lesions. There are several animal models of SVD, but they do not fully represent the spectrum of disease, often simplifying the heterogeneity seen in human tissue. By specifying human studies, we have focussed on the disease in the appropriate context. We have concentrated on sporadic SVD rather than monogenic causes which are a distinct subgroup with potentially overlapping pathophysiological mechanisms, but ultimately different phenotypes. We have, however, included CAA as part of the spectrum of SVD, further increasing the heterogeneity. The lack of precise comparisons combined with sub-optimal MRI resolutions and inconsistent reporting makes it difficult to always be sure the exact same lesions were studied and therefore have confidence in the conclusions drawn. However, we have tried to distinguish comparisons of precise cellular features from more general appearances. Inconsistent reporting also made it difficult to compare the studies, resulting in somewhat lengthy lists and descriptive results which are difficult to read and we were unable to carry out a meta-analysis. However, this is a further reflection of the variability in SVD terminology and methods.

Recently the dynamic nature of other SVD lesions including microinfarcts and lacunes has been appreciated [96]. WMH are dynamic on in vivo neuroimaging with varying outcomes [78,97,98]. These observations are, to date, not reflected in histological studies which provide only a static assessment of what are, most likely, end-stage tissue changes. In the studies in this review, the overall numbers of subjects and lesions is also very small. In future, comprehensive standardised reporting of clinical and pathological data, with precise comparison methods and advanced neuroimaging technologies are needed to study specific SVD lesions. In particular, attention to changes within and around radiological WMH should be studied; identifying the centre of a lesion and tracking changes in myelin and axons, for example, as it becomes normal appearing white matter; looking carefully for structural changes within normal appearing white matter that may be associated with WML burden. Comparing lesions in different locations and using prospective, comprehensive medical and lifestyle information will strengthen pathological–radiological–clinical associations, furthering our understanding of the pathological substrates and cellular mechanisms underlying SVD.

In summary, radiological–pathological correlation in human sporadic SVD is important, but standardised protocols and terminology in well-characterised clinical cohorts are required to truly use these correlations to advance our understanding of the pathophysiology of this common disorder. Using this systematic review and building on important definitions already published [2] we plan to undertake a multi-centre work to develop standardised definitions and grading systems that can be used to provide uniformity to future histopathological assessments of elements of sporadic SVD, similar to those developed by neuroimaging [99].

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

CAH contributed to the study concept and design, acquisition and interpretation of the data, wrote the original version of the manuscript. CS contributed to the study concept and design, interpretation of the data, critically revised the manuscript for important intellectual content, supervised the study. JMW contributed to the study concept and design, interpretation of the data, critically revised the manuscript for important intellectual content, supervised the study. The Editors of Neuropathology and Applied Neurobiology are committed to peer-review integrity and upholding the highest standards of review. As such, this article was peer-reviewed by independent, anonymous expert referees and the authors (CS) had no role in either the editorial decision or the handling of the paper.

ETHICAL STATEMENT

Ethical approval was not required for this study.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Catherine A. Humphreys https://orcid.org/0000-0003-0683-3444
Colin Smith https://orcid.org/0000-0002-4507-5132
Joanna M. Wardlaw https://orcid.org/0000-0002-9812-6642

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1

Supplementary Material

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